58-G : __ __ __

Drug Delivery in the Body Using Nanotechnology

A Look at Targeting Mechanisms Using Nanotechnology

Christina Lakomski and Christian Bach
Department of Biomedical Engineering
School of Engineering, University of Bridgeport, CT

1. Introduction

Nanotechnology is not new to science, however its rather recent implementation in drug delivery is proving to be one of the most beneficial applications of nanotechnology. In 2001, the National Nanotechnology Initiative was created. Since 2001, it has received twelve billion dollars in funds, and just last year in 2010, was allocated 1.6 billion dollars in federal funding [3]. This alone shows how important nanotechnology is to research and development.

There are several nanoparticles that can be used for targeted drug delivery. Some of them include: polymeric nanoparticles, solid lipid particles, nanocrystalline magnetic iron oxide particles, polymeric micelles, quantum dots, dendrimers, and phospholipid micelles [6].

The preferred route of drug delivery is via oral delivery, however currently that remains and issue for many drugs, and because of that they are given intravenously. However, through the use of nanoparticles and their small size, reformulation of drugs may improve their bioavailability, allowing certain drugs to be given orally [8]. Nanoparticles not only allow certain drugs to be given orally, they also allow for drugs to be given at lower doses. This is because nanoparticles allow for specific targeting, reducing the need for drugs to have to go through the blood stream to attack diseased tissue.

Biomaterials are widely used as nanoparticles. Biomaterials in the body can be used for tissue regeneration and tissue engineering [2]. Additionally, materials such as chitosan and diatoms can be used in drug delivery. These types of materials are an ideal source of nanoparticles as they reduce the need for synthetic materials as nanoparticles.

Nanoparticles are an ideal way to deliver drugs to specific diseased tissues or tumors for many reasons. They offer lower doses, and thus lower toxicities. Additionally, nanoparticles have longer circulation half lives, ensuring that the therapeutic agent will be maintained in the body, until it is unloaded at the desire site, and nanoparticles have more efficient cellular uptake [4]. Nanoparticles can infiltrate the cells of the body due to their small size, allowing for efficient unloading of the therapeutic agent being delivered.

Nanotechnology is a rapidly emerging field of science with infinite medical applications. Nanotechnology has the potential to revolutionize how physicians treat their patients, and has the potential to help improve a patient's quality of life while receiving treatments.

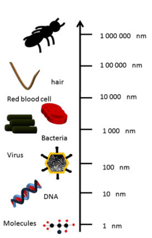

Figure 1: Shows many different molecules at the nanometer size. Nanomedicine operates at a scale of about 100 nm or less (Boisseau & Loubaton, 2011)

2. Delivery Systems

Passive targeting exploits the differences between normal and diseased tissue. It also capitalizes on the EPR (enhanced permeability and retention) effect [8]. Tumors within the body have unique characteristics. They have unique anatomical and physiological abnormalities, which are caused by the EPR effect. The EPR effect is characterized by: angiogenesis, which is the physiological process of growing new blood vessels from pre-existing blood vessels, giving tumors a much more dense vessel network. Next, tumors have defective vasculature architecture. They also have impaired lymphatic drainage systems. Lastly, tumors are known to have elevated levels of bradykinin, nitric oxide, and peroxynitrite [1]. Because we know tumors exhibit these qualities due to the EPR effect, nanoparticles can be designed to target the tumors.

Localized delivery is the direct delivery of drugs to tumors using nanoparticles. This kind of delivery system is effective or local cancers such as prostate and head and neck cancers [8]. This kind of targeting is showing promise for intracellular drugs that are considered to be pretty much insoluble, such as Taxol. It is also promising for sensitive drugs such as proteins, oliogonucleotides, and DNA.

Active targeting requires active binding to occur. It requires the binding of receptor specific ligands to specific cells in the body, which will promote site specific targeting. Active targeting can also be achieved by recognition of diseased cells, as they have signature molecules that are over expressed at diseased sites [8].

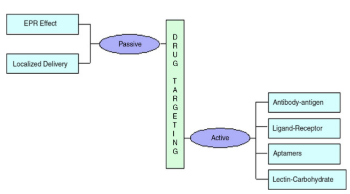

Figure 2: The schematic above details passive, localized, and active targeting, showing how nanoparticles can be delivered to the body (Sahoo et al., 2007).

Magnetic nanoparticles have the ability to help with many forms of nanotechnology. Not only for drug delivery but also for imaging. Magnetic nanoparticles have the ability to enhance proton relaxation at specific tissues [10]. This can allow targeted delivery of drugs loaded onto to the magnetic nanoparticles, as specific tissues, such as tumor tissue can be targeted by such nanoparticles. Magnetic nanoparticles can also serve as magnetic resonance imaging contrast agents [10]. Using these nanoparticles as contrast for MR imaging can help to give a better view of internal organs and tissues.

3. Personalized Medicine

Personalized medicine is the new wave of medicine. It is no longer appropriate for companies to develop drugs that only effectively treat eighty percent of patients [9]. Rather, it is now the norm to develop drugs that treat specific populations of patients. Drug responses in patients are related by two processes: pharmacodyanmics, and pharmacokinetics. Pharmacodyanmics measure the effects of the drug on the body, for example drug-receptor interactions. Pharmacokinetics measure the actions by an organism on the drug which can be drug absorption, distribution, metabolism, and elimination [12]. These measurements can give researchers more information about the mechanisms of drugs in the body. With this information, personalized drug therapies can be instituted for patients. For example, in oncology patients, gene therapy can be used to effectively treat tumors. Many cancers have been associated with DNA methylation and the progression of the disease [5]. Using nanotechnology to deliver DNA to targeted tumors has the potential to aid in reducing the progression of the cancer. It can also aid to help scientists understand the mechanism of disease progression in cancer.

Medicine can be personalized using nanotechnology. With information obtained from genomics: pharmacokinetics and pharmacodyanmics, researchers and physicians can predict how certain patient populations will react to a given therapy. It can also help to identify certain biomarkers for diseases. Given this information, treatment can be tailored to the patient. This kind of personalized medicine can reduce doses needed of drugs, eliminate the need for certain drugs that physicians know will not work for a patient, and help to reduce associated toxicities with certain treatments. Multiple lines of therapies will not be needed for certain diseases, as researchers will be able to acquire data from genomics that help to identify the most effective treatments for a specific disease.

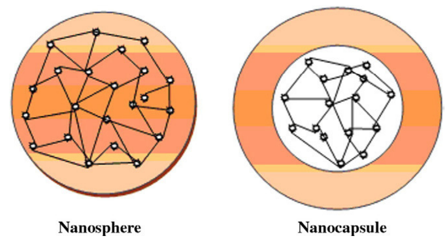

Figure 3: A schematic representing nanocarriers. Such nanocarriers can be loaded with the desired drug. Certain nanocarriers will be attracted to specific tissues based off of the EPR effect (Mishra, Patel, & Tiwari, 2010)

4. Drug Toxicities and Challenges

The use of nanotechnology can help to reduce the dose needed to treat a patient, and thus will reduce the side effects experienced by the drugs, or at the very least, to lessen the degree of the toxicity. Because nanoparticles can target specific tissues in the body, only the amount of drug that is absolutely needed has to be used. Drugs administered in the body without nanoparticles are characterized by, "their poor solubility, high toxicity, high dosage, aggregation due to poor solubility, nonspecific delivery, in vivo degradation, and short circulating half-lives," [7]. These characteristics lead to needing higher dosages to effectively treat a disease. Through the use of nanoparticles, the need for such high doses can be eliminated.

Lower doses not only lead to decreased toxicities, it also leads to an increase in a patient's quality of life. Without toxicities or with limited toxicities, patients can enjoy their lives without worrying about being nauseous or having terrible rashes. Also, through the use of nanoparticles, patients won't have to set their watch by their medication. They will have to take less medication, in less increments, without being constantly hindered by fasting or avoiding certain foods with high acidity. Loading drugs onto nanoparticles protects the therapeutic agents and helps the drug to make it to the desired tissue.

It is important to note however, that nanoparticles are not completely without their toxicities either. Nanoparticles, such as carbon nanotubes, can cause allergic reactions within the body [11]. There is also no way to be sure that the nanoparticles are going exactly to the desired area of the body, and because of their size nanoparticles can pass through many barriers. This leaves open the possibility that drug will be unloaded at the incorrect tissue.

There are no experimental procedures that are not without their potential consequences, however, even facing some possible toxicities due to the nanoparticles, the science behind nanoparticles is far more attractive than distributing the drug to patients in the traditional manner.

References:

[1] Acharya, Sarbari, and Sanjeeb K. Sahoo. "Plga Nanoparticles Containing Various Anticancer Agents and Tumour Delivery by Epr Effect." Advanced Drug Delivery Reviews 63.3 (2011): 170-83.
[2] Boisseau, Patrick, and Bertrand Loubaton. "Nanomedicine, Nanotechnology in Medicine." Comptes Rendus Physique 12.7 (2011): 620-36.
[3] Kateb, Babak, et al. "Nanoplatforms for Constructing New Approaches to Cancer Treatment, Imaging, and Drug Delivery: What Should Be the Policy?" NeuroImage 54 (2011): S106-S24.
[4] Koo, Otilia M., Israel Rubinstein, and Hayat Onyuksel. "Role of Nanotechnology in Targeted Drug Delivery and Imaging: A Concise Review." Nanomedicine: Nanotechnology, Biology and Medicine 1.3 (2005): 193-212.
[5] Labhasetwar, V. "Nanotechnology for Drug and Gene Therapy: The Importance of Understanding Molecular Mechanisms of Delivery." Current Opinion in Biotechnology 16.6 (2005): 674-80.
[6] Mishra, B., Bhavesh B. Patel, and Sanjay Tiwari. "Colloidal Nanocarriers: A Review on Formulation Technology, Types and Applications toward Targeted Drug Delivery." Nanomedicine: Nanotechnology, Biology and Medicine 6.1 (2010): 9-24.
[7] Parveen, Suphiya, Ranjita Misra, and Sanjeeb K. Sahoo. "Nanoparticles: A Boon to Drug Delivery, Therapeutics, Diagnostics and Imaging." Nanomedicine: Nanotechnology, Biology and Medicine (2011).
[8] Sahoo, S. K., S. Parveen, and J. J. Panda. "The Present and Future of Nanotechnology in Human Health Care." Nanomedicine: Nanotechnology, Biology and Medicine 3.1 (2007): 20-31.
[9] Sakamoto, Jason H., et al. "Enabling Individualized Therapy through Nanotechnology." Pharmacological Research 62.2 (2010): 57-89.
[10] Sun, C., J. Lee, and M. Zhang. "Magnetic Nanoparticles in Mr Imaging and Drug Delivery." Advanced Drug Delivery Reviews 60.11 (2008): 1252-65.
[11] Vega-Villa, Karina R., et al. "Clinical Toxicities of Nanocarrier Systems." Advanced Drug Delivery Reviews 60.8 (2008): 929-38.
[12] Vizirianakis, Ioannis S. "Nanomedicine and Personalized Medicine toward the Application of Pharmacotyping in Clinical Practice to Improve Drug-Delivery Outcomes." Nanomedicine: Nanotechnology, Biology and Medicine 7.1 (2011): 11-17.